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Clinical utility of the clinical dementia rating scale for Parkinson's disease dementia

Abstract

The purpose of this study is to explore validity of the Clinical Dementia Rating Scale (CDR) in measuring dementia among individuals with Parkinson's disease. The CDR was created for use in patients with Alzheimer's disease and, to date, there are no published studies specifically examining if the CDR is appropriate for patients with PD. The data were obtained from the National Alzheimer's Coordinating Center database (The NACC database is funded by National Institute on Aging grant number U01 AG016976). There were 490 subjects (mean/SD: Age = 72.11/9.20; education = 16.09/6.07; 73.3% male) diagnosed with dementia (n= 151), mild cognitive impairment (n= 186), or normal cognition (n = 153) by a physician. Inclusion criteria were a diagnosis of Parkinson's disease. Exclusion criteria were possible or probable Alzheimer's disease or other confounding conditions. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for the previously published CDR Global Score as well as the Sum of Boxes cutoff scores for each of the 3 diagnostic categories. Finally, new cutoff scores were calculated using sensitivity and specificity values derived from the Receiver Operating Characteristic curves. The results indicate the CDR is a useful tool in identifying dementia in patients with Parkinson's disease when the cutoff scores are adjusted.

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CLINICAL UTILITY OF THE CLINICAL DEMENTIA RATING SCALE FOR
PARKINSON'S DISEASE DEMENTIA

A DISSERTATION
SUBMITTED TO THE FACULTY
OF
SCHOOL OF PROFESSIONAL PSYCHOLOGY
PACIFIC UNIVERSITY
HILLSBORO, OREGON
BY
KATHRYN A. WYMAN-CHICK
IN PARTIAL FULFILLMENT OF THE
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Abstract

The purpose of this study is to explore validity of the Clinical Dementia Rating Scale (CDR) in measuring dementia among individuals with Parkinson's disease. The CDR was created for use in patients with Alzheimer's disease and, to date, there are no published studies specifically examining if the CDR is appropriate for patients with PD. The data were obtained from the National Alzheimer's Coordinating Center database (The NACC database is funded by National Institute on Aging grant number U01 AG016976). There were 490 subjects (mean/SD: Age = 72.11/9.20; education = 16.09/6.07; 73.3% male) diagnosed with dementia (n= 151), mild cognitive impairment (n= 186), or normal cognition (n = 153) by a physician. Inclusion criteria were a diagnosis of Parkinson's disease. Exclusion criteria were possible or probable Alzheimer's disease or other confounding conditions. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for the previously published CDR Global Score as well as the Sum of Boxes cutoff scores for each of the 3 diagnostic categories. Finally, new cutoff scores were calculated using sensitivity and specificity values derived from the Receiver Operating Characteristic curves. The results indicate the CDR is a useful tool in identifying dementia in patients with Parkinson's disease when the cutoff scores are adjusted.

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Clinical Utility of the Clinical Dementia Rating Scale for Parkinson's Disease Dementia

The purpose of this study was to calculate the sensitivity and specificity of the Clinical Dementia Rating Scale (CDR) in measuring dementia and mild cognitive impairment among individuals diagnosed with Parkinson's disease (PD). The CDR uses a semi-structured interview to rate six domains associated with Alzheimer's Disease (AD): memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. To date, there are no published studies specifically examining if the published CDR cutoff scores are appropriate for patients with PD. This paper includes an overview of neuropsychological profile of PD and Parkinson's disease dementia (PDD), as well as a review of the efficacy of similar dementia screening tools used in PDD.

According to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*, dementia is characterized by significant difficulty with social or occupational functioning caused by memory impairment and one or more of the following cognitive symptoms: aphasia, apraxia, agnosia, or executive dysfunction (American Psychiatric Association [APA], 2000). PDD is a subcortical dementia associated with the degenerative disorder PD and falls under the category of dementias due to other general medical conditions in the *DSM-IV-TR* (APA, 2000). In 2007, the Movement Disorder Study Task Force (MDSTF) was created to develop specific diagnostic criteria for PDD. According to the MDSTF, the core feature required for diagnosis of PDD is that the individual has received a diagnosis of PD at least one year prior to the development of dementia symptoms.

The statistics on incidence and prevalence of PDD in the community vary and are dependent on the age of participants, recruitment methods, and measurement tools used to assess dementia (Aarsland, 2010; Reid, Hely, Morris, Loy, & Halliday, 2011; Riedel et al., 2008;

Zakzanis, Leach, & Kaplan, 1999). Pirozzolo et al. (1982) argued that it is difficult to determine the precise prevalence rate, as many individuals with PD exhibit some degree of cognitive impairment. Riedel and colleagues (2008) examined 873 patients with PD and found the prevalence of dementia in their sample was 17.5 percent as measured by the Mini-Mental Status Exam (MMSE), 41.8 percent as measured by the Clock Drawing Test (CDT), and 43.6 percent as measured by the Parkinson Neuropsychometric Dementia Assessment (PANDA), while 28.6 percent met criteria for dementia based upon *DSM-IV-TR* criteria.

In a longitudinal study conducted by Marder, Tang, Cote, Yaakov, and Mayeux (1995), approximately 20 percent of PD patients in the sample developed dementia over the course of two years. Additionally, participants with PD were 1.7 times more likely to develop dementia than control participants after controlling for age, gender, and education (Marder et al., 1995). An Australian study conducted over the course of 20 years indicated that 83 percent of surviving participants diagnosed with PD developed dementia by 70 years of age (Reid et al., 2011).

Risk factors for PDD include low education, severity of extrapyramidal motor symptoms, and advanced age (Aarsland et al., 2005; Glatt et al., 1996; Reid et al., 2011). However, studies have provided mixed evidence to support the hypothesis that age of onset of PD is a significant risk factor for PDD (Aarsland et al., 2005; Glatt et al., 1996; Marder et al., 1995; Reid, 1992; Reid et al., 2011).

Neuropsychological Profile in Parkinson's Disease and Parkinson's Disease Dementia

Non-demented patients with PD often experience neuropsychological deficits related to the disease process, including executive dysfunction and visual-spatial problems. Additional features of PDD in addition to neuropsychological deficits of PD include psychological and behavioral characteristics. Psychological and behavioral features may include apathy, depression,

visual hallucinations, delusions, and excessive daytime sleepiness (Aarsland, Cummings, & Larsen, 2001; Emre et al., 2007; Starkstein et al., 1996). Diagnosis of PDD can be complicated due to these and other issues related to medication, depression, fatigue related to sleep disturbances and the “attribution of functional impairment due to cognitive dysfunction rather than motor disability” (Marti, Tolosa, & de la Certa, 2007; p. 43). Neuropsychological characteristics of PDD may include impairment in executive functioning, processing speed, visual-spatial and construction ability, working memory, and attention (Bronnick, 2005; Emre, 2005; Emre et al., 2007; Janvin et al., 2006). The neuropsychological symptoms associated with PD and PDD are discussed in further detail below.

Executive functions and attention. Executive functions are involved in a wide variety of tasks including engaging in goal-directed behavior and inhibiting behavior as well as planning, sequencing, shifting, and monitoring tasks (Lezak, Howieson, & Loring, 2004; Loring, 1999). Executive dysfunction is considered one of the “cognitive hallmarks” of PD (Bronnick, 2005; p33), and even non-demented patients with PD perform poorly on tests of executive functioning such as the Wisconsin Card Sorting Test and Trail Making Test B (Dubois et al., 2007). Furthermore, patients with PD and PDD perform poorly on Verbal Fluency tasks (Dubois et al., 2007; Jacobs et al., 1995; Mahieux et al., 1998).

Attention is defined as “processes that enable an individual to engage in certain cognitive operations while ignoring others” and the ability to maintain this focus (Loring, 1999; p. 24). Fluctuations in attention are common among patients with PD and PDD (Bronnick, 2005; Emre, 2005). As a result, attentional impairment may complicate the patient’s ability to perform activities of daily living (ADL; Bronnick, 2005). Additionally, deficits in executive functioning

and attention may contribute to problems with gait, leading to an increased number of falls (Hausdorff et al., 2005).

Visual-spatial ability. A core feature of PD involves a decline in visual-spatial ability over the course of the patient's lifespan (Brown & Marsden, 1986; Johnson & Galvin, 2011). It has been proposed that the decline in visual-spatial abilities evident in PD patients both with and without dementia may be due to eye movement abnormalities associated with changes in motor ability (Bodis-Wollner, 2003). Additionally, visual tasks requiring a motor component may be difficult for patients with PD (Brown & Marsden, 1986), however performance on Block Design is independently correlated with severity of dementia in patients with PD (Levin et al., 1991). In all, visual-spatial impairment is more severe in PDD than AD, however it is more severe in Lewy Body Dementia (LBD) than PDD (Bronnick, 2005).

Verbal ability. Verbal ability is described as the "acquisition and retention of stimuli that are verbal or linguistic in nature" (Loring, 1999; p. 164). Pirozzolo, Hansch, Mortimer, Webster, and Kuskowski (1982) argued that individuals with PDD tend to have normal performance on vocabulary and information verbal ability tests, as well as tests designed to detect agnosia or apraxia. Typically patients with PD have average performance on language tasks. However, as PDD progresses it may involve cortical language functions, which are reflected in tasks such as the Boston Naming Test (Dubois et al., 2007). Additionally, PDD patients may have communication deficits related to motor impairment (Bronnick, 2005), such as dysarthria (Tjaden, 2008).

Working memory. Working memory is a "limited capacity memory system that provides temporary storage to manipulate information for complex cognitive tasks such as learning and reasoning" (Loring, 1999; p. 106). Patients with PDD perform poorly on tests of

working memory such as Digit Span backward (Dubois et al., 2007; Lezak et al., 2012). On average, non-demented patients with PD do not display deficits in working memory (Zakzanis, Leach, & Kaplan, 1999).

Motor ability. Comparing performance of patients with PD to normal control groups on motor ability tasks may be confounded, as PD is characterized by movement impairment. Thus, the difference in scores may reflect the severity of motor symptoms, rather than cognitive factors such as psychomotor speed and coordination (Pirozzolo et al., 1982).

Memory. Memory problems are less prominent in patients with PDD than in other forms of dementia (Bronnick, 2005). Zakzanis et al. (1999) argued that memory problems in PDD patients are likely secondary to degeneration of the frontal lobes and executive dysfunction. Free recall is often impaired in patients with PD (Ellfolk, et al., 2012). Although delayed recall of verbal and visual material is often impaired in patients with PDD, recognition performance is generally in the normal range (Breen, 1993; Lezak et al., 2012; Tröster & Fields, 1995). Because of this, it is sometimes believed that memory performance may improve with the use of cues (Lezak et al., 2012; Tröster & Fields, 1995); however there is mixed evidence to support this (Higginson, et al., 2005). In addition, due to visual-spatial deficits, it is common for patients with PD to demonstrate impaired visual memory (Song, et al., 2008).

Psychological Profile in Parkinson's Disease

Individuals with PD frequently experience changes in psychological functioning as a result of the disease process, which often continue to affect the individual as they develop dementia. Depression, apathy, and sleep disturbance are common psychological features associated with PD (Dubious et al., 2007; Emre, 2005; Emre et al., 2007; Marsh & Friedman, 2005). Depression is often co-morbid with PDD, however it is not certain if this is part of the

degenerative process of the disease, adjustment to disability, or a combination of these factors (Stern, 2000). A study conducted by Starkstein et al. (1990) indicated that PD patients with depression have more cognitive impairment and decline more rapidly than do PD patients without depression.

In addition, Poewe (2003) stated, "All major antiparkinsonian drugs can induce psychosis in at-risk patients" (p. 580). Risk factors include advancing age, length of time since PD diagnosis, presence of depression, and severity of disease symptoms. PD patients taking dopaminergic drugs frequently experience visual hallucinations and behavioral changes including difficulty with impulse control and obsessive thoughts (Marsh & Friedman, 2005; Poewe, 2003).

Mild Cognitive Impairment in Parkinson's Disease

The International Working Group on Cognitive Impairment MCI as a condition that is neither normal nor demented but with evidence of functional decline; however, ADLs are relatively intact (Winblad et al., 2004). In 2012, the MDSTF published diagnostic criteria for MCI in PD (Litvan et al., 2012). PD-MCI may include some memory impairment unusual for age and education, but the memory impairment does not reach the level of dementia (Fernandez et al., 2005; Litvan et al., 2012). MCI is common in non-demented patients with PD (Caccappolo & Marder, 2005; Goldman & Litvan, 2011; Litvan et al., 2012). More specifically, executive dysfunction (Song et al., 2008) and visual-spatial deficits (Goldman & Litvan, 2011) frequently are found in patients with PD. However, some authors have stated there is increasing evidence to support the hypothesis that PD-MCI is a prodromal phase of PDD, despite the fact that MCI does not always evolve into full blown dementia (Goldman & Litvan, 2011; Janvin et al., 2006). Others have contended that there is not enough research to support this claim (Tröster, 2008).

The MDSTF argued that the primary difference between PD-MCI and PDD is significant functional impairment (Litvan et al., 2012). It can be difficult to identify MCI in PD patients without a clinical interview and specific screening tools, because by definition the symptoms do not interfere with ADLs (Fernandez et al., 2005). Additionally, prevalence rates of MCI in PD are not well known, as MCI is a relatively new concept and comprehensive longitudinal studies have not been conducted. The MDSTF has estimated that 19-38% of individuals with PD who are not demented meet criteria for PD-MCI (Litvan et al., 2012). A recent study conducted by Sollinger, Goldstein, Lah, Levey, and Factor (2010) examined 72 non-demented PD patients. The participants received a neurological exam and neuropsychological assessment. The results indicated that 52.8 percent met criteria for PD-MCI (Sollinger et al., 2010). This study highlights the importance of conducting research on identifying MCI in PD.

Comparison with Lewy Body Dementia

Similar to PD, LBD is a subcortical dementia. According to the MDSTF, if the cognitive symptoms appear earlier than one year after PD diagnosis, the individual meets criteria for LBD (Emre et al., 2007). While LBD and PDD are similar in their clinical profile, there is evidence to support the hypothesis that LBD and PDD are distinctly different disorders (Braak et al., 2005; Libow et al, 2009). Braak et al. (2005) argued that, at the cellular level, LBD “exhibits a clinical phenotype apparently different from PD,” however there are similarities in the brain areas affected by LBD and PD.

Comparison with Alzheimer's Disease

The neuropsychological profiles of individuals with PDD are distinctly different from individuals with AD (Aarsland, 2005; Jacobs et al., 1995; Tröster, 2008). Patients with AD experience more difficulty with memory and language (Mahieux et al., 1998), whereas individuals with PDD have greater impairment in executive functioning and attention (Anderson, 2004; Bronnick, 2005). However, it is possible for individuals with PD and PDD to have features of AD (Anderson, 2004). Unlike many patients with AD, patients with PDD typically have insight into the nature of their cognitive problems (Emre, 2005). In addition, it is possible for the two conditions to co-exist (Rajput, Rozdilsky, & Rajput, 1993).

MCI exists as a prodromal stage for both PDD and AD. A study by Matteau and colleagues (2011) measured MCI in PDD and AD using the Mattis Dementia Rating Scale (MDRS), and they determined that the PD-MCI group was different from the AD-MCI group in important ways. In this study, the participants in the AD-MCI group had memory impairment, but the PD-MCI participants had non-memory deficits in domains such as construction, attention, and conceptualization.

Neuropsychiatric symptoms are present in both PDD and AD. Aarsland, Cummings, and Larsen (2001) compared neuropsychiatric symptoms in 42 participants with PDD and 42 participants with AD. The participants were matched on age, sex, and MMSE scores. Neuropsychiatric symptoms were measured using the Neuropsychiatric Inventory. Results indicated that there were significant differences between patients with PDD and AD. In this study, patients with AD exhibited higher levels of apathy and aberrant motor behavior, whereas the PDD group had higher levels of depression and hallucinations. Although the AD group had a higher number of symptoms overall, the severity of symptoms in PDD was significantly greater

than in AD. The authors conclude that neuropsychiatric symptoms in PDD are substantially different than in AD, which may be due to distinct underlying neurobiological disease processes in the two conditions.

In 2011, the Alzheimer's Association and the National Institute on Aging of the National Institutes of Health published new criteria and guidelines for diagnosing AD. The new guidelines introduced two new stages of the disease: preclinical AD and MCI. Preclinical AD is defined as changes in biomarkers that may indicate early signs of disease before there are any symptoms in thoughts or behaviors. AD-MCI is defined as mild changes in memory that can be observed and measured but do not impair ADLs. The third stage, dementia due to AD, involves problems in memory, thinking, and behavior that impair ADLs (McKhann et al., 2011). Defining earlier stages of the disease in this way allows researchers to study diagnosis and treatment before the disease progresses.

Cognitive Screening Tools for Dementia

Many studies examining PDD use measurement tools developed for AD that do not sufficiently capture important domains such as executive dysfunction that may be present in non-AD forms of dementia (Harvey et al., 2010; Sano, 2006).

Mini-Mental Status Exam. The MMSE was created as a screening tool for dementia (Folstein, Folstein, & McHugh, 1975). In 2007, the MDSTF recommended that when the MMSE is used as a screening tool for PDD, a cutoff score of <26 be used. However they cautioned that the MMSE is not ideal for measuring executive dysfunction, which is a key feature of PDD (Dubois et al., 2007; Marti, Tolosa, & de la Cerda, 2007). Additionally, Robottom and Weiner (2009) pointed out that patients with PDD demonstrate executive dysfunction early in the disease process, and the MMSE may not be able to detect this impairment.

Mamikonyan et al. (2009) examined the use of the MMSE as a screening tool for MCI in PD. The study included 106 patients with PD who participated in neuropsychological assessment of memory, executive functioning, and attention. Results of the study suggested that impairment in memory and executive functioning are common in adults with PD and MCI. Similarly, Nazem and colleagues (2009) conducted a study using the MMSE and the Montreal Cognitive Assessment (MoCA), and a striking finding was that cognitive impairment may be present in PD patients with “normal” MMSE scores. In fact, “approximately half of patients with PD with a normal MMSE score have cognitive impairment based on the recommended MoCA cutoff score,” indicating that the MoCA may be more sensitive in detecting PD-MCI (p. 304). A study conducted by Zadikoff and colleagues (2008) also suggested the MoCA may be a better brief screening tool for cognitive deficits in PD than the MMSE.

ADAS-Cog. The Alzheimer's Disease Assessment Scale Cognitive Behavior Section (ADAS-Cog) is a brief screening tool for AD that measures word recall, naming objects, orientation, construction, and comprehension (Cano et al., 2010). Harvey et al. (2010) conducted a study of the clinical utility of the ADAS-Cog for patients with PDD. Assessments were administered at baseline and at 4-week follow-up. Participants included 55 patients with PDD and 58 patients with AD from the United States, Hungary, Italy, and France. Patients with LBD were excluded. Additionally, participants with an MMSE score of 17 or less were separated into the “moderate” group and participants with a score of 18-24 were placed in the “mild” group. The results found that ADAS-Cog scores were highly correlated with MMSE scores for patients with PDD. The ADAS-Cog also showed high test-retest reliability after a 4-week delay; however, further research is needed to determine if it is a valid tool for tracking decline in PDD over an extended period of time. The authors concluded that the ADAS-Cog is a valid tool for

the assessment of mild and moderate dementia in patients with Parkinson's disease, despite the fact it was developed for use in patients with AD (Harvey et al., 2010).

Mattis Dementia Rating Scale-2. The Mattis Dementia Rating Scale-2 (MDRS-2) is a widely used assessment tool that assesses cognitive domains affected by sub-cortical and frontal lobe dementias including attention, initiation and perseveration, and conceptualization. The MDSTF recommended the MDRS-2 in the assessment of global efficiency in patients with PD, as the MMSE is not as sensitive in detecting subcortical changes (Dubois, et al., 2007). Matteau and colleagues (2012) examined the MDRS-2 in PD patients with MCI and dementia. The results indicated the MDSR-2 is appropriate for use in individuals with MCI and dementia; however there may be a ceiling effect, which makes it difficult to identify MCI in PD. The MDRS-2 does not measure functional impairment; it is strictly a cognitive evaluation and is used in conjunction with a thorough diagnostic interview.

Clinical Dementia Rating Scale. The CDR was developed as a tool to accurately differentiate between different stages of AD. Individuals with Parkinson's disease were explicitly excluded from the original studies leading to development of the CDR (Hughes, Berg, Danziger, Cobin, & Martin, 1982). The updated CDR uses a semi-structured interview to rate performances across six domains associated with AD: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Morris, 1993). The domains are scored independently of each other, although memory is considered to be the primary category. The category with the highest ranking (i.e., greatest level of impairment) is used to determine the CDR global score (CDR-GS), which ranges between 0 and 3, where 0 = *absence of symptoms*, 0.5 = *questionable*, 1 = *mild*, 2 = *moderate*, and 3 = *severe dementia* (Hughes et al., 1982; Morris, 1993). The CDR may be an ideal staging tool for PDD, as the score reflects the impact of

cognitive impairment on daily activities and excludes physical disability as a result of the disease process.

The expanded sum of boxes score (CDR-SB) is an optional score, which uses scores from all six domains and ranges between 0-18 (Morris, 1993; O'Bryant, et al., 2010). In this score, all of the domains have equal weight. O'Bryant and colleagues (2010) used the CDR-SB to compare groups with MCI, probable AD, possible AD, LBD, vascular dementia, primary progressive aphasia, frontotemporal dementia, and "dementia other" which included alcohol-related dementia, dementia of undetermined etiology, progressive supranuclear palsy, prion disease, and Huntington's disease. The analysis did not include participants with PDD. The study included 12,462 participants from the National Alzheimer's Coordinating Center (NACC) database including 5,115 control group participants, 2,551 patients with MCI, and 4,796 patients with dementia. For AD, the CDR-SB recommended cutoff scores were as follows: 0 = *normal*, 0.5 to 4 = *questionable*, 4.5 to 9 = *mild*, 9.5 to 15.5 = *moderate*, and 16 to 18 = *severe*. The authors argued that the expanded CDR-SB is more sensitive for "tracking changes within and between stages of dementia" than the CDR-GS. They argued that the greater range of scores for the CDR-SB is more beneficial for research and clinical applications than the CDR-GS scores (O'Bryant et al., 2010; p. 748). A limitation of this study was the exclusion of patients with PDD, therefore it is not known if published CDR-SB ranges are valid for this group.

Clinical Utility of the CDR for Dementia Screening

The clinical utility, or ability of a test to accurately identify individuals with specific conditions, is critical for conducting research and evaluating patients. Sensitivity is defined as the proportion of individuals correctly classified by a test as having the condition; whereas specificity is the likelihood that the test will detect absence of the condition in individuals who

do not have the condition (Strauss, Sherman, & Spreen, 2006). Positive predictive power is the likelihood that someone with a positive test result will in fact have the condition, and negative predictive value reflects the probability that someone with a negative test result will in fact not have the condition (Glaros & Kline, 1988; Strauss, Sherman, & Spreen, 2006). Sensitivity, specificity, and predictive power are used to create representative cutoff scores using appropriate base rate characteristics of the population in question (Elwood, 1993; Glaros & Kline, 1988; Meehl & Rosen, 1955).

Glaros and Kline (1988) pointed out that, “obviously, as cutting scores are altered, sensitivity and specificity values of tests will change as well” (p. 1015). Liepelt-Scarfone and colleagues (2011) examined PD-MCI using different cut-off scores on several neuropsychological tests that measured executive function, attention, praxis and visual function, psychomotor speed, list learning and word memory recall, and logical memory. They found that more conservative cut-off scores only detected individuals with more severe symptoms and lower ADLs and therefore did not detect the PD-MCI group. They stated, “Both the frequency and clinical profile of PD-MCI patients were relevantly dependent on the cut-off value used for the definition of cognitive impairment” (p. 5).

Purpose of Current Study

The purpose of this study was to examine the sensitivity and specificity of the CDR in detecting cognitive impairment among individuals diagnosed with PD. As noted above, patients with PDD exhibit more problems with executive functions, visual-spatial functions, and attention, whereas patients with AD experience more difficulty with language and memory (Bronnick, 2005). The CDR was developed to detect AD; many of the core symptoms of PDD and AD are different, therefore there may be differences in the optimal cutoff scores for PDD

and AD. Several authors have used CDR cutoff scores developed for AD to classify stages of dementia in patients with PDD (Galvin, 2006; Galvin, Pollack & Morris, 2006; Kovari et al., 2003; Llebaria et al., 2008; Pagonabarraga et al., 2008); however to date, there are no published studies specifically examining if the published CDR cutoff scores are appropriate for patients with PD.

On one hand, the CDR scoring is weighted more heavily for memory and it does not include a formal test of visual-spatial ability or executive functions, which may limit the usefulness of this screening tool for patients with PD. On the other hand, the MDSTF concluded that, "one cornerstone of the diagnosis of dementia is the evidence of an impact on daily living activities that cannot be attributed to motor or autonomic symptoms in the case of PDD" (Dubois et al., 2007; p. 2315). The instructions for the CDR read, "Mark in only one box for each category, rating impairment as decline from the person's usual level due to cognitive loss alone, not impairment due to other factors such as physical handicap or depression" (Morris, 1993; p. 2413). Therefore, the usefulness of the CDR in the screening and staging of PDD may be enhanced by the measurement of ADLs independent of a non-cognitive disease process and executive functions in the form of judgment and decision-making. In this study, the CDR performances of three groups of patients with PD were compared: normal cognition, PD-MCI, and PDD. The main hypotheses of the study are listed below.

- Because CDR-GS cutoff scores published for AD are heavily weighted for memory and do not include visuospatial tasks, it is hypothesized that the published cutoff scores will not accurately differentiate between normal cognition, PD-MCI, and PDD.

- The expanded CDR-SB score will be more useful than CDR-GS for patients with PD, as the CDR-SB includes scores from all 6 domains and memory is not scored as the primary domain.

Method

Participants

This study was exempted from IRB oversight, as data were anonymous in the archival dataset. Participant data were obtained from the National Alzheimer's Disease Coordinating Centers (NACC) uniform data set, which includes data from 29 National Institute on Aging-Funded Alzheimer's Disease Centers (Beekly et al., 2004; Beekly et al., 2007; Weintraub et al., 2009). Informed consent was obtained by participants or their proxies at the individual centers where the patients were examined. All participants in the dataset had been examined using standardized protocols and diagnosed by experienced physicians using uniform, published guidelines (Beekley et al., 2004; Beekley et al., 2007). The NACC procedures require several quality checks of the data before they are entered into the database (Beekly et al., 2007).

Participants from the NACC database have been classified into three diagnostic categories: normal cognition, MCI, and dementia based upon physician diagnosis. Inclusion criteria for the present study were a diagnosis of PD and complete CDR scores in the dataset. Individuals with PD together with probable or possible AD were specifically excluded from the study in order to increase internal validity of the study. Data from patients with other dementia syndromes such as frontotemporal degeneration, vascular dementia, or primary diagnosis of LBD were excluded from the present study. Data from individuals with a history of stroke contributing to cognitive problems, traumatic brain injury, prion disease, brain neoplasm, multiple system atrophy, brain surgery, and normal pressure hydrocephalus were also excluded.

A total of 490 participants met inclusion criteria and were analyzed in the current study. With respect to demographic information, age and education of the participants are listed in Table 1, gender is listed in Table 2, and ethnicity is listed in Table 3.

A one-way analysis of variance (ANOVA) was conducted to evaluate significant differences in age between the three participant groups. Levene's test was significant; therefore the three groups were not homogeneous. The one-way ANOVA was significant using the Welch test [$F_{\text{asympt}}(2, 313.16) = 13.72, p < .001$]. Follow up tests were conducted to evaluate pairwise differences among the group means. The Games-Howell post-hoc test results indicated that the dementia group had a significantly higher age than the PD-MCI and normal cognition groups. There was no significant difference in age between the PD-MCI group and the normal cognition group. See Table 1 for means and standard deviations.

A one-way ANOVA also was conducted to evaluate potential differences in education between the three participant groups. The one-way ANOVA was not significant, $F(2, 487) = 2.64, p = .072$, indicating there were no significant differences in education levels among the three groups.

Table 1

Participant Age and Years of Education by Group

	Normal Cognition <i>N</i> = 153		PD-MCI <i>N</i> = 186		PDD <i>N</i> = 151	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age	70.08	10.46	71.38	8.52	75.07	7.87
Education	16.25	2.86	16.69	9.06	15.19	3.04

Note: PD-MCI = Parkinson's Disease Mild Cognitive Impairment; PDD = Parkinson's Disease Dementia

Table 2

Gender of Participants by Group

	Normal Cognition <i>N</i> = 153	PD-MCI <i>N</i> = 186	PDD <i>N</i> = 151
Male (<i>n</i> = 359)	27.8 % (<i>n</i> = 100)	38.7% (<i>n</i> = 139)	33.4% (<i>n</i> = 120)
Female (<i>n</i> = 131)	40.5% (<i>n</i> = 53)	35.9% (<i>n</i> = 47)	23.7% (<i>n</i> = 31)

Note: PD-MCI = Parkinson's Disease Mild Cognitive Impairment; PDD = Parkinson's Disease Dementia

Table 3

Number of Participants by Group

	Normal Cognition <i>N</i> = 153	PD-MCI <i>N</i> = 186	PDD <i>N</i> = 151
Caucasian <i>N</i> = 460	94.8% (<i>n</i> = 145)	91.9% (<i>n</i> = 171)	95.4% (<i>n</i> = 144)
African American <i>N</i> = 18	2.0% (<i>n</i> = 3)	4.8% (<i>n</i> = 9)	4.0% (<i>n</i> = 6)
Asian American <i>N</i> = 5	2.0% (<i>n</i> = 3)	1.1% (<i>n</i> = 2)	0% (<i>n</i> = 0)
Multiethnic <i>N</i> = 7	0.49% (<i>n</i> = 2)	2.1% (<i>n</i> = 4)	0.7% (<i>n</i> = 1)

Note: PD-MCI = Parkinson's Disease Mild Cognitive Impairment; PDD = Parkinson's Disease Dementia

Statistical Analysis

CDR-GS and CDR-SB scores from the NACC database were analyzed in this study. While multiple visits were included in the dataset for some patients, scores were obtained from participants' most recent visit only for this study in order to capture as many individuals with PD-MCI and PDD as possible, while maintaining independent observations among data analyzed. Descriptive data including means and standard deviations on the CDR-GS and CDR-SB were computed for participants with normal cognition, PD-MCI, and PDD, as well as for the sample as a whole.

Sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the diagnosis of dementia as the characteristic and various cutoff scores on the CDR-GS and CDR-SB, following procedures outlined in Strauss, Sherman, and Spreen (2006). This procedure was replicated for individuals with normal cognition and for those with a diagnosis of PD-MCI.

Receiver operating characteristic (ROC) curves were generated to depict the diagnostic accuracy of CDR-GS and CDR-SB scores in classifying MCI and dementia in patients with PD. These procedures were used to test the null hypothesis that the published CDR cutoff scores developed for AD are the same for PDD. Finally, new cutoff scores were calculated using sensitivity and specificity values derived from the ROC curves.

Results

Table 4 displays means and standard deviations of the CDR subscale scores, global score, and sum of boxes score for each group.

Table 4

Clinical Dementia Rating Scale Scores by Group

	Normal Cognition		PD-MCI		PDD	
	M	SD	M	SD	M	SD
CDR Memory	0.08	0.21	1.34	0.21	1.34	0.76
CDR Orientation	0.02	0.11	0.12	0.24	0.99	0.81
CDR Judgment	0.05	0.18	0.41	0.31	1.35	0.78
CDR Community Affairs	0.06	0.19	0.33	0.38	1.37	0.81
CDR Home and Hobbies	0.05	0.18	0.32	0.34	1.48	0.88
CDR Personal Care	0.01	0.11	0.10	0.39	1.05	1.15
CDR-GS	0.09	0.21	0.50	0.18	1.36	0.80
CDR-SB	0.27	0.77	1.78	1.26	7.59	4.65

Note: PD-MCI = Parkinson's Disease Mild Cognitive Impairment; PDD = Parkinson's Disease Dementia; CDR = Clinical Dementia Rating Scale, CDR-GS = Clinical Dementia Rating Scale Global Score, CDR-SB = Clinical Dementia Rating Scale Sum of Boxes Score

CDR-GS Sensitivity and Specificity

Tables 5-7 displays the proportion of true positives, true negatives, false positives, and false negatives for classification of those with normal cognition, PD-MCI, or PDD based on the results of previously published CDR-GS cutoff scores (Morris, 1993).

Table 5

Sensitivity and Specificity of Clinical Dementia Rating Scale Global Score Published Norms in Participants with Normal Cognition

	Participants with Normal Cognition	Participants with abnormal cognition	
CDR-GS indicates normal cognition (0-.5)	151	206	PPV = 42.3%
CDR-GS is within abnormal range (>1)	2	131	NPV = 98.4%
	Sensitivity = 98.7%	Specificity = 38.9%	

Note: CDR-GS = Clinical Dementia Rating Scale Global score; PPV = Positive Predictive Value; NPV = Negative Predictive Value

Table 6

Sensitivity and Specificity of Clinical Dementia Rating Scale Global Score Published Norms in Participants with Mild Cognitive Impairment

	Participants with PD-MCI	Participants without PD-MCI	
CDR-GS indicates MCI (1)	12	69	PPV = 14.8%
CDR-GS outside of MCI range (0-.5, 2-3)	174	255	NPV = 59.4%
	Sensitivity = 6.5%	Specificity = 78.7%	

Note: CDR-GS = Clinical Dementia Rating Scale Global score; PD-MCI = Parkinson's Disease Mild Cognitive Impairment; PPV = Positive Predictive Value; NPV = Negative Predictive Value

Table 7

Sensitivity and Specificity of Clinical Dementia Rating Scale Global Score Published Norms in Participants with Dementia

	Participants with PDD	Participants without PDD	
CDR-GS indicates dementia (2-3)	52	0	PPV = 100%
CDR-GS does not indicate dementia (≤ 1)	99	339	NPV = 77.4%
	Sensitivity = 34.4%	Specificity = 100%	

Note: CDR-GS = Clinical Dementia Rating Scale Global score; PDD = Parkinson's Disease Dementia PPV = Positive Predictive Value; NPV = Negative Predictive Value

CDR-GS ROC Curve

ROC curve analyses were conducted for the CDR-GS for each group. Figures 1-3 display the discriminant properties of the CDR-GS score (left line) for each diagnosis against the reference line (diagonal line). According to the ROC curve for CDR-GS, a cutoff score of 0 yielded the best sensitivity and specificity (.84 and .98, respectively) for the normal cognition group. The Area Under the Curve (AUC) was 0.07 (95% CI = 0.05-0.10). A CDR-GS score of .05 yielded the best sensitivity and specificity for the PD-MCI group (.88 and .82, respectively). The AUC was 0.51 (95% CI = 0.56-0.56). Finally, for individuals with PDD, a CDR-GS of >1 yielded the best sensitivity and specificity (.79 and .96, respectively). The AUC was 0.92 (95% CI = 0.90-0.95).

Figure 1. Receiver Operator Characteristics Curve Analysis: Clinical Dementia Rating Scale Global Score for Normal Cognition

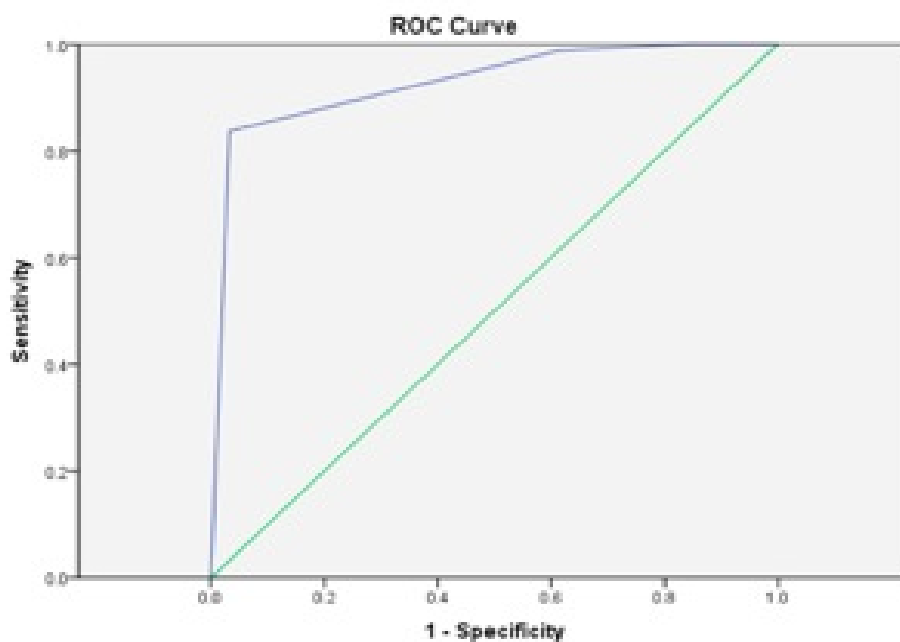


Figure 2. Receiver Operator Characteristics Curve Analysis: Clinical Dementia Rating Scale Global Score for Mild Cognitive Impairment

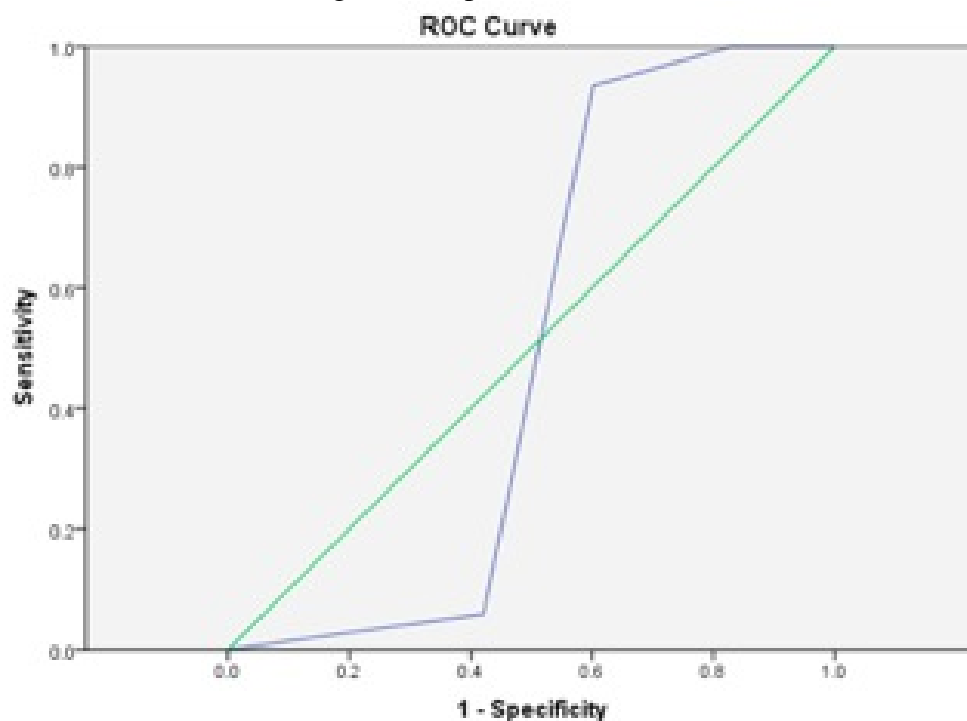
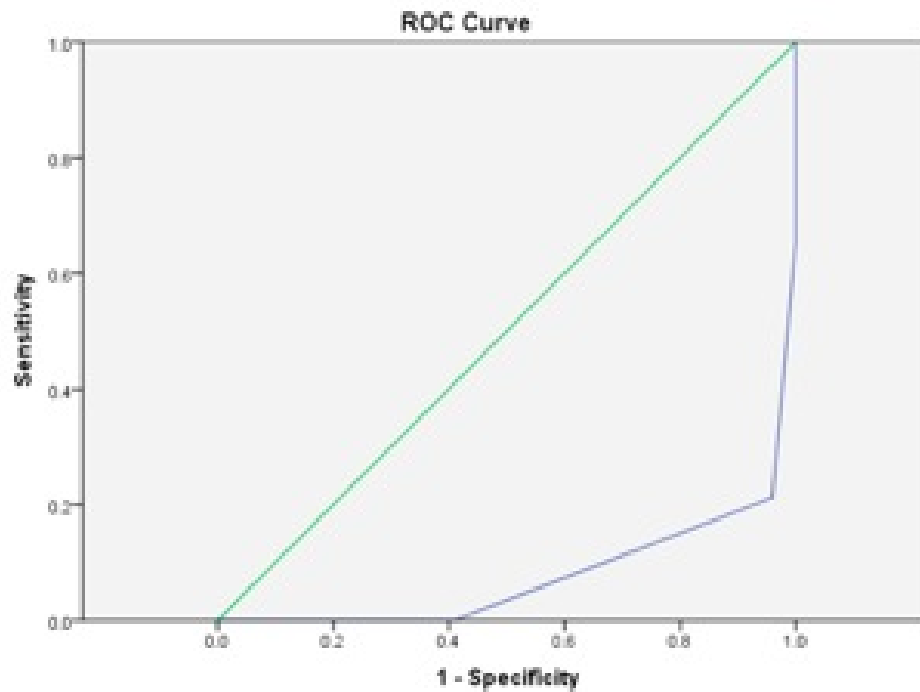


Figure 3. Receiver Operator Characteristics Curve Analysis: Clinical Dementia Rating Scale Global Score for Dementia



CDR-SB Sensitivity and Specificity

Tables 8-10 displays the proportion of true positives, true negatives, false positives, and false negatives for classification of those with normal cognition, PD-MCI, or PDD based on the results of published CDR-SB cutoff scores (Morris, 1993; O'Bryant, et al., 2010).

Table 8

Sensitivity and Specificity of Clinical Dementia Rating Scale Sum of Boxes Score Published Norms in Participants with Normal Cognition

	Participants with Normal Cognition	Participants with abnormal cognition	
CDR-SB indicates normal cognition (.5-4)	152	43	PPV = 77.9%
CDR-SB is within abnormal range (>4.5)	1	294	NPV = 100%
	Sensitivity = 99.3%	Specificity = 87.2%	

Note: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes score; PPV = Positive Predictive Value; NPV = Negative Predictive Value

Table 9

Sensitivity and Specificity of Clinical Dementia Rating Scale Sum of Boxes Score Published Norms in Participants with Mild Cognitive Impairment

	Participants with PD-MCI	Participants without PD-MCI	
CDR-SB indicates MCI (4.5-9)	144	61	PPV = 70.2%
CDR-SB outside of MCI range (0-4, 9.5- 18)	42	247	NPV = 85.5%
	Sensitivity = 77.4%	Specificity = 80.2%	

Note: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes score; PD-MCI = Parkinson's Disease Mild Cognitive Impairment; PPV = Positive Predictive Value; NPV = Negative Predictive Value

Table 10

Sensitivity and Specificity of Clinical Dementia Rating Scale Sum of Boxes Score Published Norms in Participants with Dementia

	Participants with PDD	Participants without PDD	
CDR-SB indicates dementia (9.5-18)	52	0	PPV = 100%
CDR-SB does not indicate dementia (≤ 9)	99	339	NPV = 77.4%
	Sensitivity = 33.8%		Specificity = 100%

Note: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes score; PDD = Parkinson's Disease Dementia; PPV = Positive Predictive Value; NPV = Negative Predictive Value

CDR-SB ROC Curve

ROC curve analyses were conducted for the CDR-SB for each group. Figures 4-6 display the discriminant properties of the CDR-SB score (left line) for each diagnosis against the reference line (diagonal line). In individuals with normal cognition, a CDR-SB score between 0-.5 yielded the best sensitivity and specificity (.91 and .87, respectively). The AUC was 0.05 (95% CI = 0.03-0.07). For the CDR-SB, a score between 1-4 provided the best sensitivity and specificity (.71 and .82, respectively) in individuals with PD-MCI. The AUC was 0.48 (95% CI = 0.43-0.54). Finally, for individuals with PDD, the ideal CDR-SB cutoff score is ≥ 4.5 , which yielded the best sensitivity and specificity (.74 and .98, respectively). The AUC was 0.97 (95% CI = 0.96-0.98).

Figure 4. Receiver Operator Characteristics Curve Analysis: Clinical Dementia Rating Scale Sum of Boxes Score for Normal Cognition

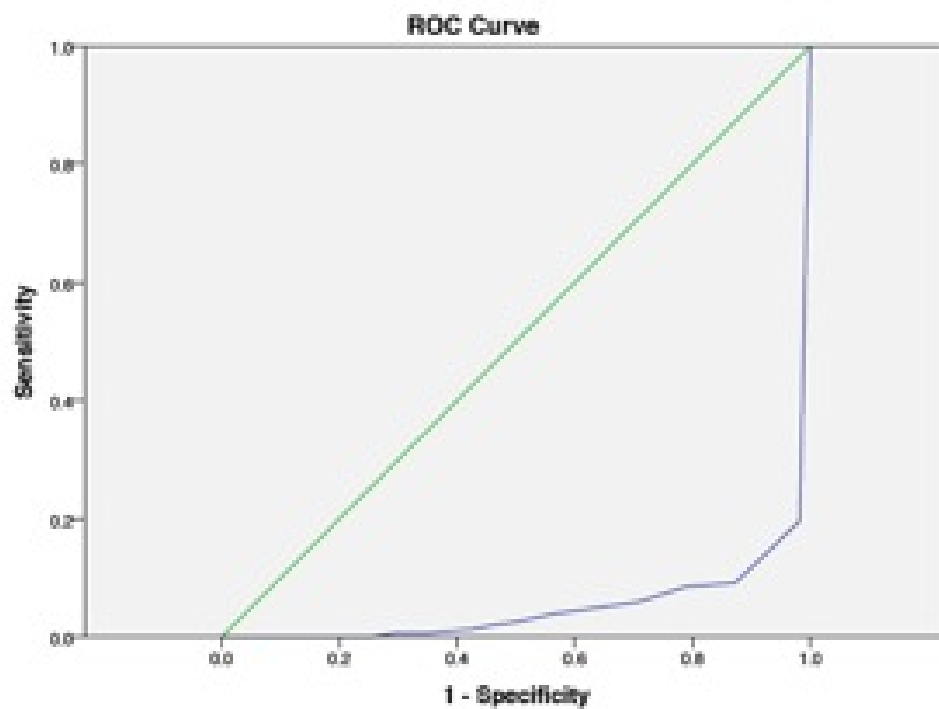


Figure 5. Receiver Operator Characteristics Curve Analysis: Clinical Dementia Rating Scale Sum of Boxes Score for Mild Cognitive Impairment

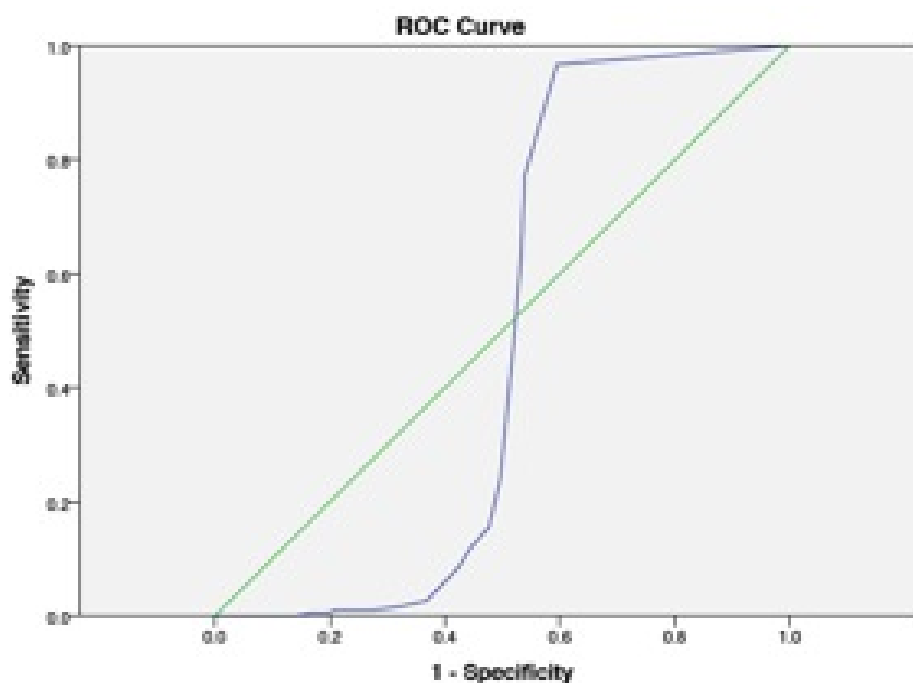
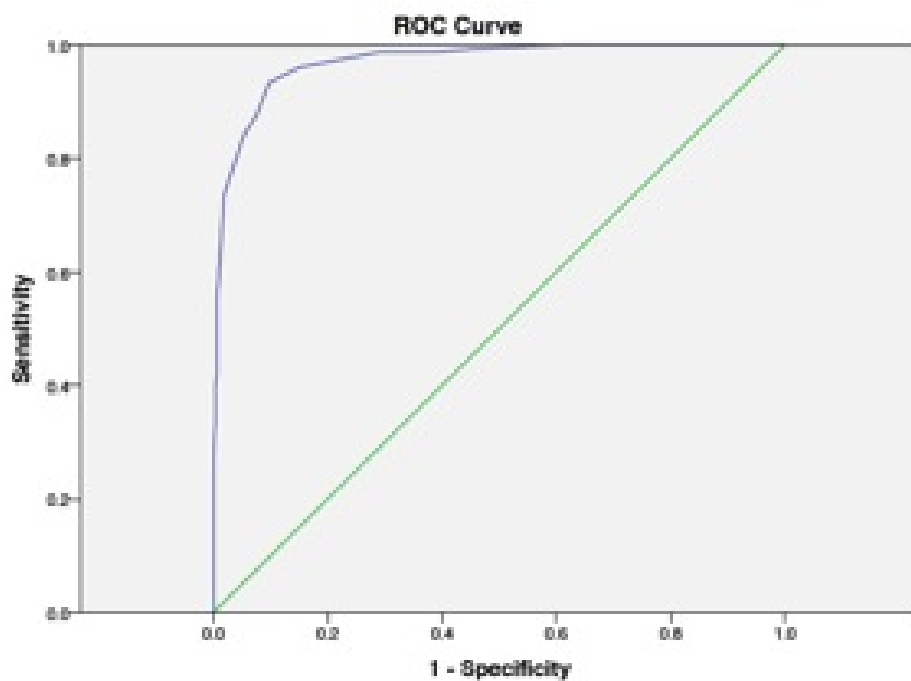


Figure 6. Receiver Operator Characteristics Curve Analysis: Clinical Dementia Rating Scale Sum of Boxes Score for Dementia



Overall Sensitivity and Specificity for the CDR

Table 11 displays a comparison of CDR cutoff scores published by the test developers and the recommended CDR cutoff scores for individuals with PD found in this study. Table 12 provides sensitivity and specificity values for published cutoff scores in individuals with PD and sensitivity and specificity values for the recommended cutoff scores found in this study. The recommended values for CDR-GS normal cognition found in this study had a slightly lower sensitivity value than for published scores, however specificity has increased. For the CDR-SB, sensitivity values for the normal and PD-MCI groups were slightly lower than for published scores, however this was considered acceptable as a trade-off for increasing sensitivity and specificity for the dementia group.

Table 11

A Comparison of Clinical Dementia Rating Scale Published Cutoff Scores and Recommended Cutoff Scores for Parkinson's Disease Found in this Study

	CDR-GS		CDR-SB	
	Published cutoff scores	Recommended cutoff scores	Published cutoff scores	Recommended Cutoff Scores
Normal Cognition	0-0.5*	0	0-4**	0-0.5
PD-MCI	1	0.5	4.5-9	1-4
PDD	2-3	≥ 1	9.5-18	≥ 4.5

Note: CDR-GS = Clinical Dementia Rating Scale Global Score; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes Score; MCI = Parkinson's Disease Mild Cognitive Impairment; PDD = Parkinson's Disease Dementia

*0.5 = "questionable" impairment

** 0-4 = "questionable" impairment

Table 12

Comparison of Sensitivity and Specificity Values for the Clinical Dementia Rating Scale for Patients with Parkinson's Disease

	CDR-GS		CDR-SB	
	Published cutoff scores Sensitivity/ Specificity	Recommended cutoff scores Sensitivity/ Specificity	Published cutoff scores Sensitivity/ Specificity	Recommended Cutoff Scores Sensitivity /Specificity
Normal Cognition	.99/.39	.84/.98	.99/.87	.91/.87
PD-MCI	.07/.79	.88/.82	.77/.80	.71/.82
PDD	.34/1.0	.79/.96	.34/1.0	.74/.98

Note: CDR-GS = Clinical Dementia Rating Scale Global Score; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes Score; PD-MCI = Parkinson's Disease Mild Cognitive Impairment; PDD = Parkinson's Disease Dementia

Discussion

The results indicate that the CDR is a useful tool in identifying dementia in patients with PD when the cutoff scores are adjusted. The present findings on the CDR compare favorably to sensitivity and specificity values of the MDRS-2 for dementia (sensitivity = 1.0; sensitivity = 1.0) and for MCI (sensitivity = 0.86; sensitivity = 0.54; Matteau, et al., 2012); however the CDR does not measure cognitive impairment in the same way as the MDRS-2. The MDRS-2 objectively measures cognitive functioning, and the CDR uses a diagnostic interview to assess functional impairment. It is important to note the CDR is a brief screening tool and it is not adequate for assessing all cognitive and functional domains. More detailed neuropsychological evaluation may be necessary for differential diagnosis. Further studies may examine the use of the MDRS-2 together with the CDR to measure cognitive changes in PD.

The first hypothesis in the study was upheld. The CDR-GS published cutoff scores did not accurately categorize individuals with MCI or dementia; however, individuals with normal cognition were accurately categorized. The second hypothesis was partially upheld. The expanded CDR-SB scores were more useful than CDR-GS scores for patients with PD; however, this was only true for the PD-MCI group. The CDR-SB did not have greater sensitivity/specificity for the group with dementia. However, if the cutoff scores are adjusted, the CDR-GS and CDR-SB appear to be useful screening tools for normal cognition, MCI, and dementia in individuals with PD.

Strengths

One strength of this study is the large sample size that appears to be similar in many ways to the general population of individuals with PD. A study conducted by Baba et al. (2005) examined 1,264 individuals with PD and male participants made up 67% of the sample. In this study, 73.3% of the sample was comprised of male participants. Baba et al. (2005) argued, "Gender may be an important factor related to the expression of PD features during the symptomatic disease course" (p. 1201).

Another strength is the quality of NACC data. All of the participants in this study were diagnosed with PD by a physician and received a cognitive evaluation to diagnose their cognitive status (i.e., normal cognition, MCI, or dementia). These detailed examinations allowed researchers to exclude cases with mixed etiology from this study in order to gain a pure sample of individuals affected by PD.

Limitations

While every attempt was made to exclude cases with mixed etiology, a limitation of this study is the lack of neuropathological confirmation, as patients with PD may also have Lewy

bodies or amyloid plaques and neurofibrillary tangles, causing additional neuropathologic changes (Anderson, 2004; Braak et al., 2005). Therefore, generalization of these findings to individuals with mixed-etiology dementias should be made with caution.

Age is a significant risk factor for dementia in PD (Aarsland et al., 2005). In this study, the patients with PDD were significantly older than patients with PD-MCI and the patients with normal cognition. There was no significant difference in age between the PD-MCI group and the normal cognition group.

Morris et al. (2006) highlighted that the participants in the NACC database agreed to participate in longitudinal research studies at academic medical centers and may underrepresent the full range of individuals in the community who meet criteria for dementia. Weintraub et al. (2009) additionally noted that one limitation of the NACC dataset is that the participants are highly educated; therefore the data may not apply to the general population. In this study, the mean level of education was equivalent to a bachelor's degree, and education may protect patients with PD from the early effects of cognitive decline (Glatt et al., 1996).

In the present study, 93.9% of the participants were Caucasian. A large-scale study conducted among US Medicare beneficiaries indicated that Caucasian participants were 50% more likely to have PD than African American or Asian participants (Wright Willis et al., 2012). However, the sample in the present study may not accurately reflect the distribution of PD among individuals from different ethnic backgrounds and is a major limitation of this study. Several barriers exist in the recruitment of older adults from culturally diverse backgrounds for participation in research including the sampling approach used by the research coordinators: lack of culturally relevant incentives for participation, history of discrimination in healthcare settings, mistrust of involvement in research due to historical events (e.g., Tuskegee), and lack of

community involvement of the institutions conducting research (Feldman et al., 2008). The data utilized in this study were archival and therefore it was impossible to address such recruiting issues in this study. However, it would be important for future researchers utilizing community samples of patients with PD to develop culturally relevant methods of recruiting participants from culturally diverse backgrounds in order to reflect the general population of patients with PD.

Summary

In summary, the present study supports the use of the CDR in patients with PD when the cutoff scores are adjusted. This provides researchers and clinicians a means of measuring the various stages of cognitive impairment in individuals with PD. Future research should focus on replicating this study in community samples.

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Appendix A

Subject Initials _____

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):					
0					
0.5					
1					
2					
3					

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.